REMARKS

Entry of the foregoing, reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. §1.112, are respectfully requested in light of the remarks which follow.

I. Claim Amendments

By the foregoing amendment, claim 1 has been amended to incorporate the subject matter of claim 7. Thus, no new matter is presented herein. Claim 7 is canceled herein without prejudice or disclaimer. Applicants reserve the right to file one or more continuation and/or divisional applications directed to any canceled subject matter. Entry of the foregoing amendments of the above-identified application are respectfully requested.

II. Response to Rejection Under 35 U.S.C. § 102

Claims 1, 16, 19-27, 30-34, 40 and 41 have been rejected under 35 U.S.C. 102(e) as purportedly anticipated by Wickham et al. ("Wickham"). Applicants respectfully submit that Wickham does not recite each and every element of the presently claimed invention.

Wickam discloses adenoviral fiber mutants that are modified to exhibit a reduced ability to bind native cellular receptors (see for example column 5 lines 1-6 of Wickham). To this end, the example section of Wickham illustrates fiber mutants that are impaired in binding to the primary CAR receptor. Wickham further discloses a number of Ad5 fiber mutants that were constructed (see Table 1 columns 17-18). Specifically, three fiber mutants exhibit modifications in position 506 (deletion of the modification of the Lys residue in position 506), 508 (substitution of the His residue in position 508 by an Ala residue (H(508)A)) and 555, (substitution of the Ser residue in position 555 by an Asn residue in combination with the substitution of the native Ser residue in position 551 (S(551)N+S(555)N)). However, when tested for CAR binding, none of these mutations demonstrated a reduced affinity for CAR receptor (and thus these mutations are not listed in Table 2).

In contrast, the presently claimed invention, as amended herein, is directed to an adenoviral fiber modified so as to exhibit a reduced ability to bind the secondary cellular receptors containing glycosaminoglycans (HGS) or sialic acid, wherein the modification(s) comprises the substitution of the Lys residue in position 506 by a Gln (K(506)Q), the substitution of the His residue in position 508 by a Lys (H(508)K) and/or the substitution of the Ser residue in position 555 by a Lys (S(555)K).

Accordingly, the fiber mutants of the present claims are not disclosed in Wickam. Applicants request that this rejection be withdrawn.

III. Claim Rejections Under 35 U.S.C. § 103

Claims 1, 16, 19-27, 29-34, 40 and 41 have been rejected under 35 U.S.C. 103(a) as purportedly unpatentable over Wickham in view of Seth et al. ("Seth"). To establish a *prima facie* case of obviousness, three basic criteria must be met. (MPEP § 2143) First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

As discussed above, Wickham discloses fiber mutants modified at positions 506, 508 and 555, (*i.e.*, mutants del K(506), H(508)A and S(551)N+S(555)N). Wickam experimentally demonstrated that these particular residues are not involved in binding to the cell surface CAR receptor. As shown in Table 2, the mutants do not exhibit a decreased CAR binding. In fact, the results of the competition assays discussed in Wickham revealed that residues that are important for receptor binding are in fact located at positions 408, 409, 412-417, 420, 474-477 and 487-492 of the native Ad5 fiber protein. Thus, according to the teaching of Wickham, the skilled artisan would be taught that the fiber residues in positions 506, 508 and 555 are either hidden in the fiber 3D structure or not available at all for interaction.

Seth fails to remedy the deficiencies of Wickham. Seth discloses an adenovirus-mediated method of plasmid transfection through a co-internalization process of plasmid DNA. Gene expression is significantly increased when plasmid transfection is performed in the presence of adenovirus or empty capsids (see

example 10; columns 25 and 26), especially when bound to the cellular receptor (see example 5 column 19). However, there is no indication in Seth as to how adenovirus interacts with the native cellular receptors, which amino acid residues are involved in this interaction, and how the adenovirus capsid proteins could be modified to alter receptor binding.

In contrast to the combined teachings of Wickham and Seth, the present invention, as amended herein, is directed to a modified adenoviral fiber comprising the substitution of the Lys in position 506 by a Gln, the substitution of the His in position 508 by a Lys and/or the substitution of the Ser in position 555 by a Lys. As experimentally demonstrated by competition assays with soluble heparin (see present Example 1), the claimed fiber mutants exhibit a reduced ability to interact with receptors containing glycosaminoglycans (HGS). The HSG-impaired mutants may be retargeted to a target cell using a targeting ligand inserted in the fiber or another capsid protein (see Example 2). Thus, the present invention provides an unexpected benefit compared to the fiber mutants disclosed in Wickham.

Accordingly, Wickam failed to disclose or suggest the role of fiber residues 506, 508 and 555 in binding cellular receptors. Further, Wickham failed to provide any guidance to the skilled person to the specific modifications recited in presently amended claim 1. Upon reviewing Wickam, the skilled artisan would have been reluctant to test additional substitutions at positions 506, 508 and/or 555 because mutations at these locations do not exhibit the required properties (alteration of interaction with the cellular receptors). Seth does not remedy Wickham because Seth is silent as to adenovirus interacts with the native cellular receptors, which amino acid residues are involved in this interaction, and the type of mutations that alter receptor binding.

Thus, Applicants request that this rejection be withdrawn.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this Amendment and Reply, or the application in general, it would be appreciated if the Examiner would telephone the undersigned attorney at 703-838-6563 concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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